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<p>(54) Title: PREPARATION OF BIARYL COMPOUNDS</p> <p>(57) Abstract</p> <p>A method for the preparation of biaryl compounds is disclosed which comprises contacting an aromatic halide in the presence of a catalyst comprising zerovalent nickel, a bidentate phosphorus-containing coordinating ligand and a reducing metal in a polar, aprotic solvent system for a time and under conditions suitable for the formation of biaryl compound.</p>		

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Description
PREPARATION OF BIARYL COMPOUNDS

This application is a continuation-in-part of
5 Serial No. 277,826, filed November 30, 1988, now
pending.

The present invention relates to the preparation of
biaryl compounds from aryl halides. In a particular
aspect, the present invention relates to the reductive
10 coupling of aryl halides.

Background of the Invention

It is known that biphenyl compounds can be produced
by the reductive coupling of aryl halides. For example,
15 Chao, et al., in the Journal of Organic Chemistry,
Volume 48, at pages 4904-4907 (1983), disclose the
reaction of aryl halides with an equivalent amount of a
highly activated metal such as nickel powder.

An alternative approach is to activate an aryl
20 halide by a chemical transformation, and then allow the
activated aryl halides to couple to form biaryl species.
For example, Gilman, et al., in the Journal of the
American Chemical Society, Volume 61, at pages 957-959
(1939), demonstrated this approach by the reaction of
25 two equivalents of aryl Grignard reagents with one
equivalent of nickel(II) salts to give biaryl compounds.
This reaction is believed to proceed through the
bis(aryl)nickel(0) species which then decomposes to give
the desired biaryl product.

30 Kumada, et al., in Bulletin of the Chemical Society
of Japan, Volume 49, at pages 1958-1969 (1976), have
demonstrated that aryl halides can be reacted with a
variety of aliphatic Grignard reagents to give alka-aryl
products. However, attempts to couple aryl Grignard
35 reagents with aryl halides were successful only with

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aryl bromides. Attempts to use aryl chlorides gave less than a ten percent yield of desired biaryl products.

Aryl chlorides are frequently more readily available than are the corresponding bromides and iodides. The chlorides are also typically less reactive and are less expensive materials as well. It would, therefore, be desirable to find a means to promote the coupling of aryl chlorides to produce high yields of biaryl compounds.

Such coupling of aryl chlorides has been disclosed by Colon, et al., in U.S. 4,263,466. The authors disclose the use of a metallic reducing agent such as zinc, magnesium, or manganese in a dipolar, aprotic solvent such as dimethylformamide with a catalyst containing a nickel compound in combination with triaryl organophosphines and alkali metal halide promoters. The reducing metal converts the nickel salts into highly reactive zerovalent nickel compounds which promote the coupling of the aryl halides and regenerate the nickel salts which can be reduced again to the zerovalent state, thereby maintaining the catalytic cycle.

In later publications by the same authors (see Colon, et al., in Journal of Organic Chemistry, Vol. 51 at pages 2627-2637 (1986), it is indicated that bidentate ligands (as opposed to the monodentate triaryl organophosphines disclosed in '466) are not effective for the nickel/reducing metal-promoted reductive coupling reaction. Takagi, et al., in the Bulletin of the Chemical Society of Japan, at pages 1887-1890 (1984) have made similar observations. See especially Run Number 14 reported at page 1888.

Statement of the Invention

In accordance with the present invention, it has surprisingly been found that aryl chlorides can be

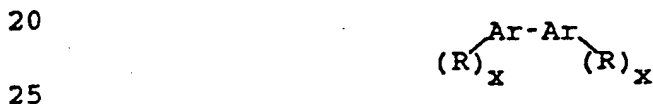
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reductively coupled employing bidentate ligands to produce biaryl compounds in high yield. By contacting aryl halides with a catalyst comprising a nickel compound, at least one bidentate phosphorus-containing
5 ligand selected from a specified group and a reducing metal, high yields of biaryl compounds are obtained.

The practice of the present invention allows for the ready preparation of biaryl derivatives from aryl chloride starting materials. Aryl chlorides are
10 generally preferred starting materials as they are more accessible on a commercial basis and are generally less expensive than the corresponding aryl bromides or aryl iodides.

15 Detailed Description of the Invention

In accordance with the present invention, there is provided a method for the preparation of biaryl compounds of the structure:



wherein Ar is an aromatic moiety having in the range of 4 up to 20 carbon atoms, each R is independently
30 selected from alkyl, aryl, -F, -NR'₂, -CN, -CHO, -OR', -OCO-R', -COO-R', $\overset{\text{O}}{\underset{\text{||}}{\text{C}}}$ -R', -SO₂-R', -SO₃R', or
35 -NR'COR':

40 wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms, and x is an integer falling in the range of 0 up to 8, depending on the size of the aromatic ring, Ar, and with the proviso that
45 there be no more than one substituent ortho to the Ar-Ar bond.

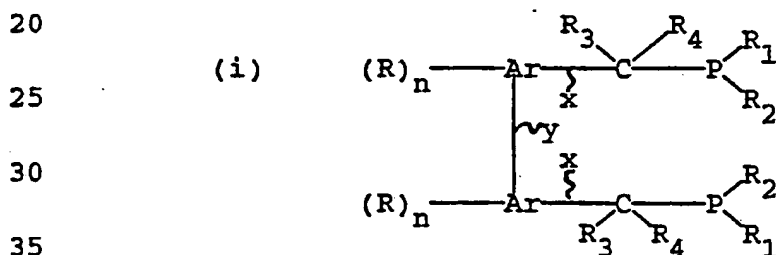
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The invention method comprises contacting an aromatic halide having the structure:



10 wherein Ar, R and x are as defined above and X is a halogen; under conditions suitable for the formation of the desired biaryl compound in the presence of at least 0.001 equivalents of a nickel catalyst comprising:

- 15 I) an anhydrous nickel compound,
 II) at least one bidentate phosphorus-containing ligand selected from the group consisting of:



40 wherein each Ar is independently selected from aromatic ring compounds having 6 up to 14 carbon atoms, e.g., phenyl, naphthyl, phenanthryl or anthracenyl;

45 the x bonds and the y bonds are attached to adjacent carbon atoms on the ring structures;

- 5 -

each R, when present as a substituent, is independently selected from alkyl, aryl, -F, -NR'₂, -CN, -CHO, -OR', -OCO-R',

5 -COO-R', -C(=O)-R', -SO₂-R', -SO₃-R', or
10 -NR'COR':

wherein R' is a hydrocarbyl or heteroaryl
15 radical having up to 20 carbon atoms;

n is a whole number in the range of 0-4
where Ar is phenyl; 0-6 where Ar is
naphthyl; and 0-8 where Ar is phenanthryl or
20 anthracenyl;

each R₁ and R₂ is independently selected
from alkyl, aryl, aralkyl, alkaryl or
cycloaliphatic radicals, or substituted
25 derivatives thereof wherein substituted
derivatives include ethers, amines, amides,
sulfonic acids, esters, hydroxyl groups and
alkoxy groups;

30 each R₃ and R₄ is independently selected
from hydrogen and the R₁ substituents;

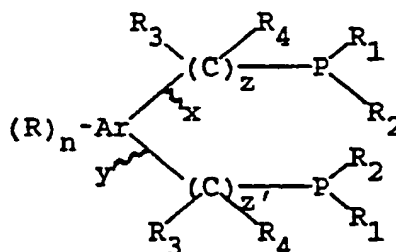
each of the above alkyl groups or moieties
is straight or branched chain of 1-20
35 carbons;

each aryl group contains 4-20 ring carbons;
and

40 each cycloaliphatic group contains from 4-8
ring carbons;

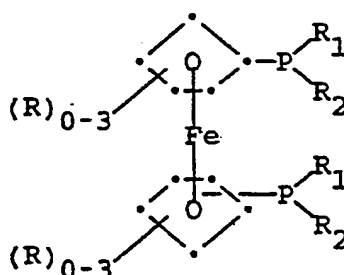
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(ii)



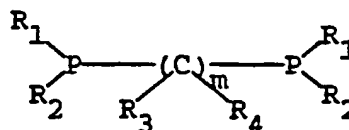
wherein Ar, x, y, R, n, R₁, R₂, R₃, and R₄ are each as defined above, and each of z and z' can independently vary between 0 and 4, with the proviso that z+z' is at least 2;

(iii)



wherein R, R₁, and R₂ are as defined above; and

(iv)



wherein R₁, R₂, R₃, and R₄ are as defined above; and m is a whole number which can vary from 4 up to 8; preferably from 5 up to 8;

as well as mixtures of any two or more of said type (i), (ii), (iii), or (iv) organophosphines; and

III) at least one reducing metal selected from

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the group consisting of zinc, magnesium and manganese,

5 wherein said contacting is carried out in a polar, aprotic, solvent system for a time and under conditions suitable for the formation of the desired biaryl compound.

Reaction temperatures employed in the practice of the present invention can vary widely. Typically, 10 reaction temperatures fall in the range of about 0 up to 250°C, with reaction temperatures in the range of about 25 up to 120°C being preferred.

Reaction times contemplated for the practice of the present invention can vary widely. One of skill in 15 the art can readily determine that amount of time which is sufficient to allow formation of the desired biaryl or heterobiaryl compounds. Typically, reaction times will fall in the range of about 0.1 up to 24 hours or longer, with reaction times in the range of about 0.5 up 20 to 16 hours being preferred.

Aryl halides contemplated for use in the practice of the present invention are compounds have the general structure:



30 wherein Ar is an aromatic moiety having in the range of 4 up to 20 carbon atoms, each R is independently selected from alkyl, aryl, -F, -NR'₂, -CN, -CHO,

35 -OR', -OCO-R', $\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{-R'}$, -SO₂R', SO₃R', or NR'COR':

40 wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms; X is a halogen and x is an integer falling in the range of 0 up to 8, depending on the size of the aromatic ring, Ar, and with the further

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proviso that there be no more than one substituent ortho to the halogen moiety. Exemplary aryl halides contemplated for use in the practice of the present invention include:

- 5 2-chlorotoluene,
- 2-bromotoluene,
- 4-chlorotoluene,
- 4-bromotoluene,
- 2-chloro-4-methylnaphthalene,
- 10 2-bromo-4-methylnaphthalene,
- 4-chloroanisole,
- 4-bromoanisole,
- 4-chlorophenylacetate,
- 4-bromophenylacetate,
- 15 2-chlorobenzyl(2-methoxy)ethyl ether,
- 2-bromobenzyl(2-methoxy)ethyl ether,
- 2-chlorobenzyl methyl ether,
- 2-bromobenzyl methyl ether,
- 2-chlorobenzyl ethyl ether,
- 20 2-bromobenzyl ethyl ether,
- 2-chlorothiophene,
- 2-bromothiophene,
- 2-chloropyridine,
- 2-bromopyridine,
- 25 2-chloro-3-methylnaphthalene,
- 2-bromo-3-methylnaphthalene,
- 1-chloro-2-methylnaphthalene,
- 1-bromo-2-methylnaphthalene,
- 1-methyl-2-chloronaphthalene,
- 30 1-methyl-2-bromonaphthalene,
- 4-fluoro-2-chlorotoluene,
- 4-fluoro-2-bromotoluene,
- 4-(N-ethyl-N-acetyl)-2-chlorotoluene,
- 4-(N-ethyl-N-acetyl)-2-bromotoluene,

6-(N-ethyl-N-acetyl)-2-chlorotoluene,
6-(N-ethyl-N-acetyl)-2-bromotoluene,
and the like, as well as mixtures of any two or more
thereof.

5 Presently preferred monohalides contemplated for
use in the practice of the present invention include
compounds having the structural formula:



wherein one or more of the carbon atoms of the benzene ring in formula (I) is optionally replaced by N;

25 wherein X is a halogen selected from the group
consisting of Cl, Br and I;

30 R is a monovalent radical selected from alkyl, aryl, -F, -NR'₂, -CN, -CHO, -OR', -OCO-R, -COO-R', $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{-R'}$, -SO₂-R', -SO₃-R', or -NR'COR':

35 wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms, and x is an integer having values of 0 to 4 with the proviso that no more than one R is in a position ortho to the X-containing ring carbon atom.

40 Additional compounds contemplated by the above structural formula are those wherein one or more of the carbon atoms of the benzene ring is replaced by N. Especially preferred compounds contemplated by the above formula are those wherein X is Cl.

45 Examples of preferred monohalides which satisfy
structural formula (I) include:

2-chlorotoluene,
2-chloropyridine,
4-fluoro-2-chlorotoluene,

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2-chlorobenzyl methyl ether,
2-chlorobenzyl ethyl ether,
4-(N-ethyl-N-acetyl)-2-chlorotoluene,
6-(N-ethyl-N-acetyl)-2-chlorotoluene,
5 4-chlorotoluene,
4-chloroanisole,
2-chlorobenzyl(2-methoxy)ethyl ether,
as well as mixtures of any two or more thereof.

A wide range of nickel compounds are suitable for
10 use in the practice of the present invention, so long
as the nickel compounds employed are essentially
water-free. The nickel(II) halide salts are a
convenient source of nickel as such compounds are
readily available in anhydrous form. Alternatively,
15 hydrates of such compounds can be employed if an
appropriate means of water removal, e.g., azeotropic
distillation, is employed prior to contacting the
nickel species with the reducing metal and aryl halide.
Those of skill in the art recognize that a wide variety
20 of nickel compounds can be used in addition to the
nickel(II) halides, e.g., nickel nitrates, sulfates,
phosphates, oxides, carbonates, carboxylates,
acetylacetonate and the like, as well as Ni(0) complexes
such as, for example, bis(1,5-cyclooctadienyl)nickel(0),
25 nickel(0) tetracarbonyl, and the like.

The nickel(II) halides are presently preferred
because of their ready availability in anhydrous form
(or, alternatively, the ease with which the hydrates
forms such compounds can be dehydrated), and because the
30 presence of halides in the reaction mixture appears to
promote the coupling reaction. Especially preferred are
nickel chloride and nickel bromide.

Suitable ratios of nickel to aryl halides can
vary widely. Molar ratios in the range of 0.0001 up to
35 0.5:1 are generally suitable. Ratios in the range of

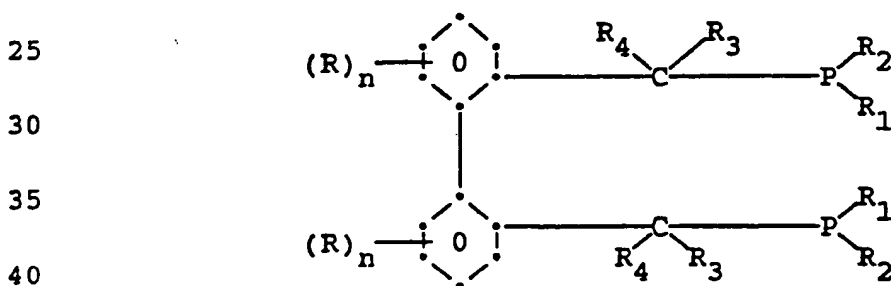
about 0.01 up to 0.2:1 are preferred, with molar ratios in the range of about 0.03 up to 0.1 being most preferred because good conversions are obtained at reasonable reaction rates.

5 Optionally added to the catalyst composition are inorganic salt promoters. When used, preferred promoters include alkali, alkaline earth, zinc, magnesium, manganese and aluminum halides, or mixtures thereof. Bromides are particularly preferred. The
10 amount of promoter, when used, can range from about 0.1 to about 1000 moles per gram atom of nickel with about 1 to about 100 moles of promoter being preferred.

The presently most preferred promoters include alkali metal iodides, alkali metal bromides and alkali metal chlorides.

Organophosphines contemplated for use in the practice of the present invention are compounds having the structures set forth above as (i), (ii), (iii), or (iv).

20 Exemplary compounds contemplated by structure (i)
include compounds having the structural formula:



45 wherein R, R₁, R₂, R₃, R₄, and n are as defined
above; including such compounds as

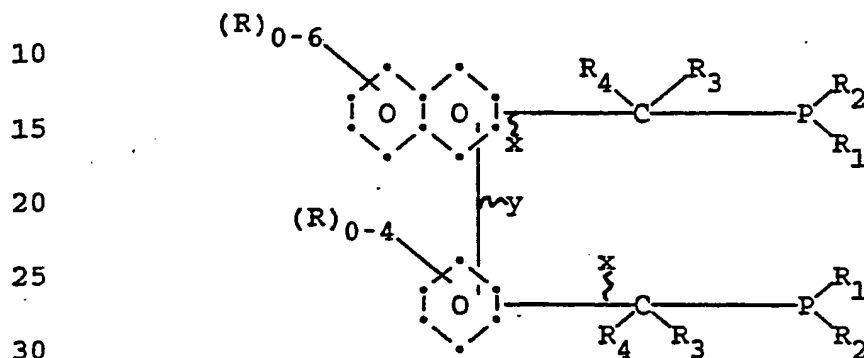
2,2'-bis(diphenylphosphinomethyl)-1,1'-biphenyl;
2,2'-bis(dibenzylphosphinomethyl)-1,1'-biphenyl;

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2,2'-bis(phenylbenzylphosphinomethyl)-1,1'-
biphenyl; and

2,2'-bis(diisobutylphosphinomethyl)-1,1'-biphenyl.

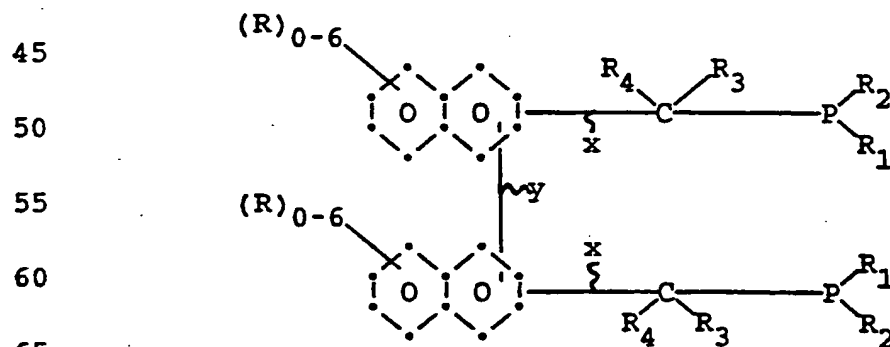
Exemplary compounds contemplated by structure (i)
also include compounds having the structural formula:



wherein R, R₁, R₂, R₃, R₄, x and y are defined
above; such as, for example

2-(diphenylphosphinomethyl)-1-[2-(diphenyl-
phosphino-methyl)phenyl]naphthalene.

Exemplary compounds contemplated by structure (i)
also include compounds having the structural formula:

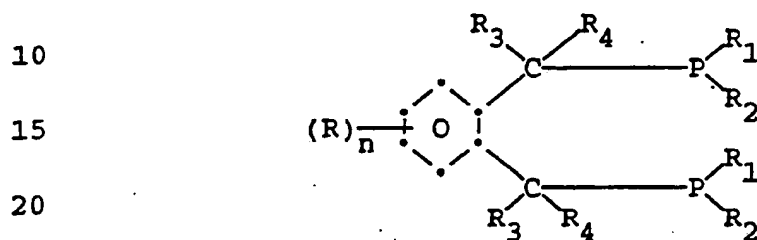


wherein R, R₁, R₂, R₃, R₄, x and y are as defined
above; such as, for example

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2,2'-bis(diphenylphosphinomethyl)-1,1'-
binaphthyl.

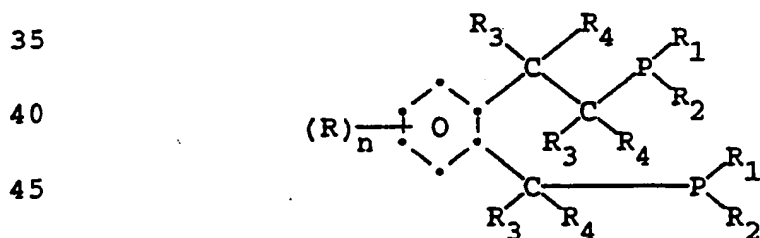
5 Exemplary compounds contemplated by structure
(ii) include compounds having the structural formula:



25 wherein R, R₁, R₂, R₃, R₄ and n are as defined
above; such as, for example

α,α'-bis(diphenylphosphino)ortho-xylene.

30 Exemplary compounds contemplated by structure (ii)
also include compounds having the structural formula:

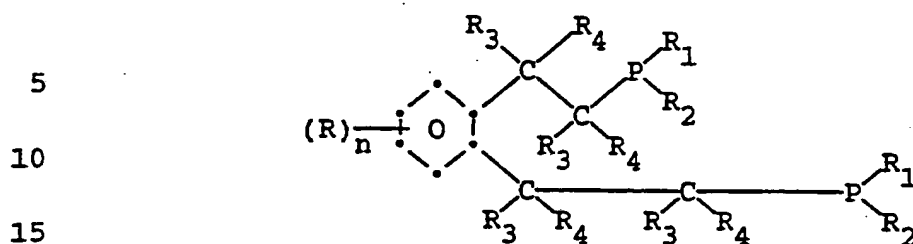


55 wherein R, R₁, R₂, R₃, R₄ and n are as defined
above; such as, for example

α,β'-bis(diphenylphosphino)-2-ethyltoluene.

Exemplary compounds contemplated by structure (ii)
also include compounds having

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20 wherein R, R₁, R₂, R₃, R₄ and n are as defined above; such as, for example

1,2-bis[2-(diphenylphosphino)ethyl]benzene.

25 Exemplary compounds contemplated by structure (iii) include: 1,1'-bis(diphenylphosphino)ferrocene, and the like.

Exemplary compounds contemplated by structure (iv) include:

30 1,4-bis(diphenylphosphino)butane,
1,5-bis(diphenylphosphino)pentane, and
35 1,6-bis(diphenylphosphino)hexane;

as well as mixtures of any two or more thereof. Also contemplated are mixtures of any two or more of said
40 type (i), (ii), (iii) or (iv) organophosphines.

The molar ratio of organophosphine to nickel compound employed in the practice of the present invention can vary widely. Typically, such molar ratio will fall within the range of 0.5:1 up to 20:1, with
45 ratios in the range of 1:1 up to 10:1 preferred. Ratios in the range of about 1:1 up to 3:1 are presently most preferred because little added benefit is seen in the use of large excesses of organophosphine(s).

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Optional coordinating ligands employed in combination with the above-described bidentate organophosphines are bidentate ligands containing at least one nitrogen atom as part of an aromatic ring structure. Such bidentate ligands include bipyridine, a C₁ up to C₆ dialkylamino pyridine, phenanthroline or 2-picolinic acid, and the like.

When the optional use of mixtures of bidentate organophosphine and bidentate ligand containing at least one nitrogen atom as part of an aromatic ring structure are employed as the coordinating ligand, molar ratios of the bidentate organophosphine to the bidentate ligand containing at least one nitrogen atom as part of an aromatic ring structure can vary widely, for example, in the range of about 0.1:1 up to 20:1, with ratios in the range of 0.5 up to 10 preferred. Ratios in the range of about 1:1 up to 2:1 are presently most preferred because little added benefit is observed when large excesses of the bidentate ligand containing at least one nitrogen atom as part of an aromatic ring structure are employed.

Solvents suitable for use in the practice of the present invention include dipolar, aprotic solvents such as solvents, such as N,N-dimethylacetamide, N,N-dimethylformamide, 1-methyl-2-pyrrolidinone, tetramethylurea, dimethylsulfoxide, sulfolane, and the like. If desired these dipolar, aprotic solvents can be mixed with lower polarity inert solvents, such as saturated aliphatic hydrocarbons, including pentanes, hexanes, dodecanes and the like; aromatic hydrocarbons, such as benzene, toluene, xylenes and the like; and saturated aliphatic and cycloaliphatic ethers, such as, diethyl ether, diglyme, tetrahydrofuran and the like.

It is preferred that all solvents use in the practice of this invention be anhydrous.

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Although magnesium and manganese metals can be used, zinc metal is the presently preferred reducing metal for use in the invention process for coupling aryl monochlorides.

5 The molar ratio of reducing metal to aryl halide employed in the practice of the present invention can vary widely. Typically, such molar ratio will fall within the range of about 0.01:1 up to 20:1, with ratios in the range of about 0.2:1 up to 10:1
10 preferred. Ratios in the range of about 0.4:1 up to 5:1 are presently most preferred because it is desired to minimize the quantity of reducing metal which must be removed from the reaction mixture and little added benefit is obtained when large excesses of reducing
15 metal are employed.

 The molar ratio of reducing metal to nickel employed in the practice of the present invention can vary widely. Typically, such molar ratios will fall within the range of about 1 up to 1000:1, with ratios
20 in the range of about 10 up to 500:1 being preferred. Ratios in the range of about 40 up to 100:1 are presently preferred for the same reasons as stated in the preceding paragraph.

 Preparation of the novel catalyst composition is
25 carried out conveniently by mixing the aforementioned nickel compound, ligand(s), promoter, and reducing metal(s) in the dipolar, aprotic solvent under an inert atmosphere and heating to a temperature in the range of about 25° to about 80°C.

30 The present invention will now be described in greater detail by reference to the following non-limiting examples.

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EXAMPLES

All reactions were conducted under an inert atmosphere. Glassware was dried prior to use and
5 flushed with nitrogen. Commercial materials were used when possible and the following were used as purchased: Anhydrous nickel(II) bromide, sodium bromide, anhydrous dimethylformamide, and zinc powder (-325 mesh). Organophosphine ligands were purchased or prepared by
10 methods known by those of skill in the art.

Typical Experimental Procedure

Nickel(II) bromide (0.22 g, 1 mmol), the desired phosphine ligand (1.5 to 3 mmol), sodium bromide (3 g),
15 anhydrous dimethylformamide (DMF; 15 mL), zinc powder (3 g, 45 mmol) and an aryl halide (20 mmoles) were combined under a nitrogen atmosphere and heated to 70°C for 14 to 16 hours. The mixture was cooled to ambient and analyzed by conventional chromatography techniques.
20 In those cases where the DMF solvent may obscure one of the products, the reaction mixture was partitioned between aqueous ammonium chloride and ethyl acetate. The organic phase was then analyzed by normal procedures.

25 Results of numerous runs with different aryl halides and different phosphine ligands are summarized in Tables I, II and III.

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Table I

Reductive Dimerization of 2-Chlorotoluene Using
Linear Bidentate Phosphines, $(\text{Ph})_2\text{P}-(\text{CH}_2)_m-\text{P}(\text{Ph})_2^*$

	Phos- phine <u>m =</u>	Mmole Ligand	[P]/ [Ni] ¹	% Convn of 2-CT ²	% Selectivity, <u>2,2'-Bitolyl</u>
5					
10	1	1.5	3	0	0
	2	1.5	3	24.9	97.8
	3	1.5	3	9.4	100
	4	1.5	3	100	94.9
	5	1.5	3	100	96.1
15	6	1.5	3	100	95.4

*All runs were carried out at 70°C for 16 hours using
 1 mmol NiBr₂, 30 mmol zinc, 3.0 grams of NaBr,
 20 mmol of 2-CT in 15 mL DMF and ligand as noted.

1) Atomic ratio of phosphorus to nickel.

2) 2-CT = 2-chlorotoluene

These results demonstrate that for linear
 bidentate phosphines of the type (iv), m must be at
 least 4, i.e., there must be at least 4 carbon atoms in
 the chain between the phosphine units. Chain lengths
 longer than 4 carbon atoms are seen to be particularly
 effective.

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Table II

Reductive Dimerization of Halotoluenes to Bitolyls*

	<u>Aryl Halide</u>	<u>% Convn</u>	<u>% Selectivity to</u>		<u>%</u>
			<u>Toluene</u>	<u>Dimers</u>	<u>Expected Dimer</u>
5	2-Chlorotoluene	100	<0.5	100	98.9 ¹
10	2-Bromotoluene	100	4.85	95.15	97.7 ¹
	3-Iodotoluene	100	10.8	89.2	80.4 ²

15 *All runs were conducted at 70°C for 16 hours using 1 mmol NiBr₂, 30 mmol zinc, 20 mmol aryl halide, 3.0 g of NaBr in DMF (15 mL). The ligand for all of these runs was 2,2'-bis(diphenylphosphinomethyl)-1,1'-biphenyl (BISBI; 1.5 mmol).

20 ¹Expected dimeric product is 2,2'-bitolyl.

²Expected dimeric product is 3,3'-bitolyl.

25 These results demonstrate that aryl chlorides are preferred starting materials for the invention reductive coupling reaction because they give the desired products in high yields with very high selectivity, without producing significant levels of reduced mono-aromatic product (i.e., toluene) or isomerized product (e.g., 2,3'-bitolyl).

30

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Table III

The Reductive Dimerization of Substituted
Aryl Halides to Substituted Biaryl Derivatives*

				% Selectivity ²		% Expected
	<u>Aryl Halide</u>	<u>Ligand¹</u>	<u>% Convn</u>	<u>H-Aryl</u>	<u>Dimers</u>	<u>Isomeric Dimer³</u>
5						
10	4-Bromo-anisole	OXYL	100	11.4	88.6	62.7
15	4-Bromo-anisole	BISBI	99.7	4.6	95.4	75.3
	4-Chloro-benzotri-fluoride	OXYL	85.9	3.7	96.3	98.7
20	4-Chloro-benzotri-fluoride	BISBI	100	2	98	98.7
25	4-Chloro-benzoni-trile	OXYL	100	16.5	83.5	79.7
30	4-Chloro-benzoni-trile	BISBI	100	5.2	94.8	72.9
	Methyl-3-chloro-benzoate	OXYL	100	7.9	92.1	93.3
35	Methyl-3-chloro-benzoate	BISBI	100	3.8	96.2	89.2
40	2-Chloro-aceto-phenone	OXYL	88.9	43.2	56.8	66.6
45	2-Chloro-aceto-phenone	BISBI	100	9.5	90.5	54.5

Table III (Continued)

5 The Reductive Dimerization of Substituted
Aryl Halides to Substituted Biaryl Derivatives*

10	<u>Aryl Halide</u>	<u>Ligand</u> ¹	<u>% Convn</u>	<u>% Selectivity</u> ² <u>H-Aryl</u> <u>Dimers</u>	<u>% Expected</u> <u>Isomeric</u> <u>Dimer</u> ³
	4-Chloro-benzaldehyde	OXYL	100	60 40	100
15	4-Chloro-benzaldehyde	BISBI	100	19.7 80.3	100
20	1-Bromo-2-methylnaphthalene	BISBI	28.8	3.6 96.4	100
25	1-Bromo-3-fluorobenzene	BISBI	100	<0.5 99.5	100

30

*All runs were carried out at 70°C for 16 hours using
 1 mmol NiBr₂, 30 mmol zinc, 20 mmol aryl halide,
 3.0 g NaBr, 1.5 mmol of ligand in DMF (15 mL).

35

1) OXYL = α,α' -bis(diphenylphosphino)ortho-xylene.

BISBI = 2,2'-bis(diphenylphosphinomethyl)-1,1'-biphenyl

40

2) H-Aryl is the reduction product of the aryl halide wherein the halogen has been replaced with a hydrogen.

45

Dimers refers to all aromatic-aromatic coupling products.

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Table III (Continued)

The Reductive Dimerization of Substituted
Aryl Halides to Substituted Biaryl Derivatives*

5

*3) Expected isomeric dimer of:

10

4-bromoanisole is 4,4'-dimethoxybiphenyl;

4-chlorobenzotrifluoride is 4,4'-bis(trifluoromethyl)biphenyl;

15

4-chlorobenzonitrile is 4,4'-dicyanobiphenyl;

methyl-3-chlorobenzoate is the dimethyl ester of 3,3'-diphenyldicarboxylic acid;

20

2-chloroacetophenone is 2,2'-diacetylbiphenyl;

4-chlorobenzaldehyde is 4,4'-diphenyldicarboxaldehyde;

25

1-bromo-2-methylnaphthalene is 2,2'-dimethyl-1,1'-binaphthyl; and

1-bromo-3-fluorobenzene is 3,3'-difluorobiphenyl.

30

- 23 -

The data in Table III demonstrate that a wide variety of functional groups are compatible with the invention process.

5 The invention has been described in detail with particular reference to preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

10

Claims

We Claim:

5 1. A method for coupling aryl and heteroaryl
monohalides having 4 to 20 carbon atoms to
produce biaryl or hetero-biaryl compounds,
said method comprising contacting said
monohalide with a catalytic combination
10 comprising:

(I) an anhydrous nickel compound, wherein the ratio of gram atoms of nickel to moles of monohalide is in the range of about 0.0001 up to 0.5;

(II) at least one bidentate phosphorus-containing ligand selected from the group consisting of

20

(i)

Chemical structure (i) shows a bisphosphine compound. It consists of two phosphorus atoms, each bonded to two R groups (R₁, R₂ and R₃, R₄). The phosphorus atoms are connected to two central Ar groups via a vertical bond (labeled y) and two diagonal bonds (labeled x). The Ar groups are also bonded to R groups (R_n).

40 wherein each Ar is independently selected
from aromatic ring compounds having 4 up to
20 carbon atoms;

45 the x bonds and the y bonds are attached to
adjacent carbon atoms on the ring
structures;

- 25 -

each R, when present as a substituent, is independently selected from alkyl, aryl,

-F, -NR'₂, -CN, -CHO, -OR', -OCO-R',

5

-COO-R', -C(=O)-R', -SO₂-R', -SO₃R',

10

or -NR'COR':

15

wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms;

20

n is an integer in the range of 0-4 where Ar is phenyl; 0-6 where Ar is naphthyl; and 0-8 where Ar is phenanthryl or anthracenyl;

25

each R₁ and R₂ is independently selected from alkyl, aryl, aralkyl, alkaryl or cycloaliphatic radicals, or substituted derivatives thereof wherein substituted derivatives include ethers, amines, amides, sulfonic acids, esters, hydroxyl groups and alkoxy groups;

30

each R₃ and R₄ is independently selected from hydrogen and the R₁ substituents;

35

each of the above alkyl groups or moieties is straight or branched chain of 1-20 carbon atoms;

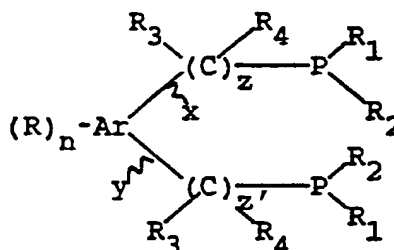
40

each aryl group contains 4-20 ring carbon atoms; and

each cycloaliphatic group contains from 4-8 ring carbons;

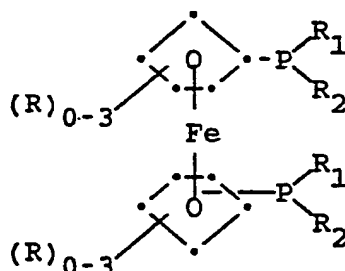
- 26 -

(ii)



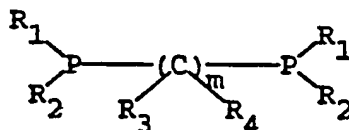
wherein Ar, x, y, R, n, R₁, R₂, R₃ and R₄ are each as defined above, and each of z and z' can independently vary between 0 and 4, with the proviso that z+z' is at least 2;

(iii)



wherein R, R₁ and R₂ are as defined above; and

(iv)



wherein R₁, R₂, R₃ and R₄ are as defined above; and m is a whole number which can vary from 4 up to 8;

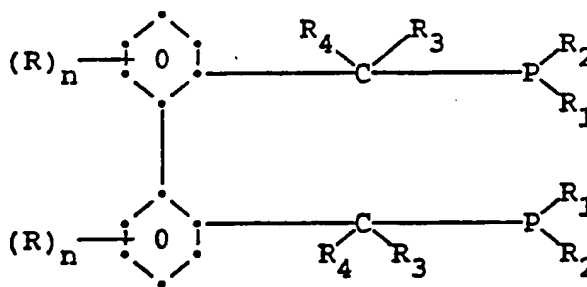
as well as mixtures of any two or more thereof; wherein the amount of ligand is in the range of about 0.5 up to 20 moles per gram atom of nickel; and

- 27 -

(III) at least one reducing metal selected from the group consisting of zinc, magnesium and manganese; wherein the molar ratio of reducing metal to reactant monohalide falls in the range of about 0.01 up to 20:1;

wherein said contacting is carried out in the presence of a polar, aprotic solvent at a temperature in the range of 0 up to 250°C for a time sufficient to form said biaryl or heterobiaryl compounds.

2. The method in accordance with Claim 1 wherein said bidentate ligand has the structural formula:



wherein R, R₁, R₂, R₃, R₄ and n are as defined above.

3. The method in accordance with Claim 2 wherein said bidentate ligand is selected from the group consisting of:

2,2'-bis(diphenylphosphinomethyl)-1,1'-biphenyl;

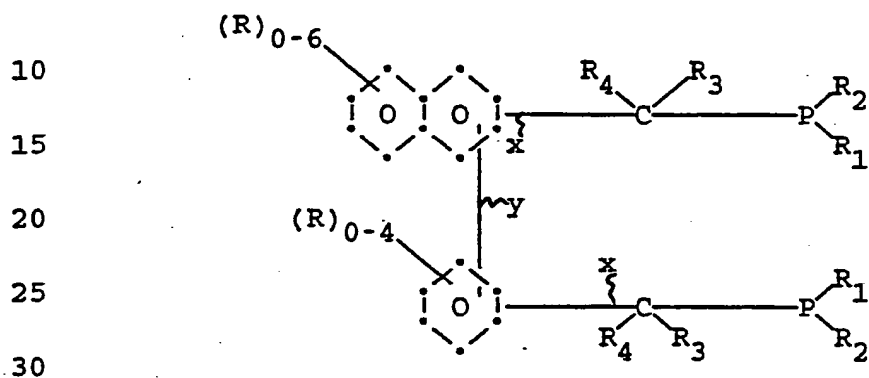
2,2'-bis(dibenzylphosphinomethyl)-1,1'-biphenyl;

2,2'-phenylbenzylphosphinomethyl)-1,1'-biphenyl; and

- 28 -

2,2'-bis(diisobutylphosphinomethyl)-1,1'-
biphenyl.

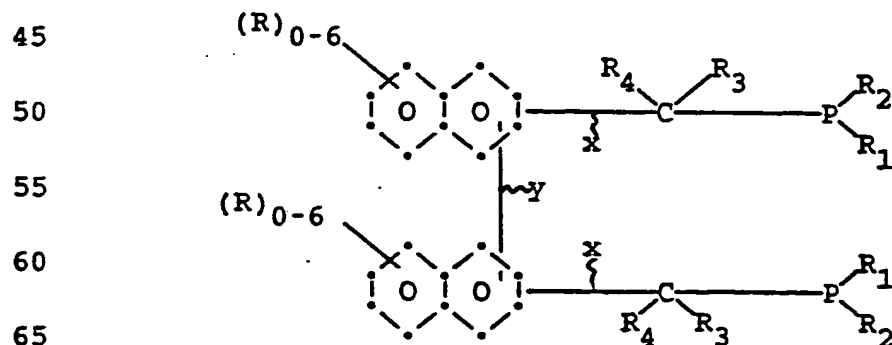
4. The method in accordance with Claim 1 wherein said
bidentate ligand has the structural formula:



wherein R, R₁, R₂, R₃, R₄, x and y are as defined
above.

5. The method in accordance with Claim 4 wherein said
bidentate ligand is 2-(diphenylphosphino-
methyl)-1-[2-(diphenylphosphinomethyl)phenyl]-
naphthalene.

6. The method in accordance with Claim 1 wherein said
bidentate ligand has the structural formula:

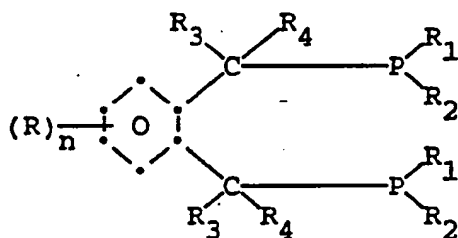


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wherein R, R₁, R₂, R₃, R₄, x and y are as defined above.

7. The method in accordance with Claim 6 wherein said
5 bidentate ligand is 2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthyl.

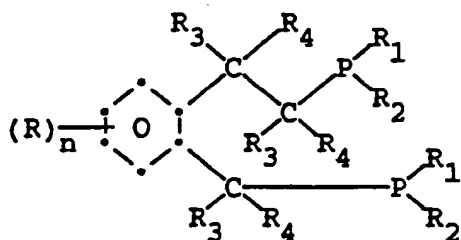
8. The method in accordance with Claim 1 wherein said
10 bidentate ligand has the structural formula:



wherein R, R₁, R₂, R₃, R₄ and n are as defined above.

9. The method in accordance with Claim 8 wherein said
35 bidentate ligand is α,α'-bis(diphenylphosphino)ortho-xylene.

10. The method in accordance with Claim 1 wherein said
40 bidentate ligand has the structural formula:

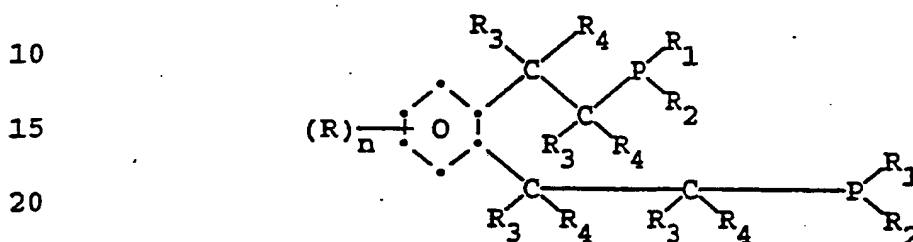


wherein R, R₁, R₂, R₃, R₄ and n are as defined above.

- 30 -

11. The method in accordance with Claim 10 wherein said bidentate ligand is α, β' -bis(diphenylphosphino)-2-ethyltoluene.

- 5 12. The method in accordance with Claim 1 wherein said bidentate ligand has the structural formula:

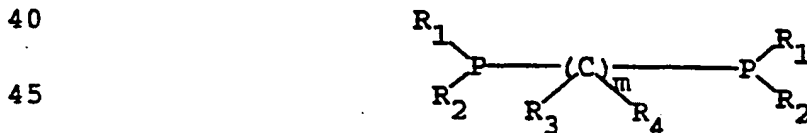


wherein R, R₁, R₂, R₃, R₄ and n are as defined above.

13. The method in accordance with Claim 12 wherein said bidentate ligand is 1,2-bis[2-(diphenylphosphino)ethyl]benzene.

14. The method in accordance with Claim 1 wherein said bidentate ligand is 1,1'-bis(diphenylphosphino)ferrocene.

15. The method in accordance with Claim 1 wherein said bidentate ligand has the structural formula:



wherein R₁, R₂, R₃ and R₄ are as defined above; and wherein m is a whole number which can vary from 4 up to 8.

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16. The method in accordance with Claim 15 wherein said bidentate ligand is selected from the group consisting of:

5 1,4-bis(diphenylphosphino)butane,
 1,5-bis(diphenylphosphino)pentane,
 1,6-bis(diphenylphosphino)hexane,

as well as mixtures of two or more thereof.

10

17. The method in accordance with Claim 1 wherein said catalytic combination further comprises at least one bidentate ligand containing at least one nitrogen atom as part of an aromatic ring structure.

15

18. The method in accordance with Claim 17 wherein said bidentate ligand containing at least one nitrogen atom is selected from 2,2'-bipyridine, a C₁ up to C₆ dialkylamino pyridine, phenanthroline or 2-picolinic acid.

20

19. The method in accordance with Claim 1 wherein said reducing metal is zinc.

25

20. The method in accordance with Claim 1 wherein the nickel compound is nickel chloride.

21. The method in accordance with Claim 1 wherein at least 0.1 moles per gram atom of nickel of an inorganic salt is added as a promoter.

30

22. The method in accordance with Claim 21 wherein the inorganic salt is selected from the group consisting of: an alkali metal iodide, an alkali

35

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metal bromide, an alkali metal chloride, as well as mixtures of any two or more thereof.

23. The method in accordance with Claim 1 wherein the
5 aprotic solvent is N,N-dimethylacetamide.

24. The method in accordance with Claim 1 wherein the aprotic solvent is N,N-dimethylformamide.

10 25. The method in accordance with Claim 1 wherein the aprotic solvent is 1-methyl-2-pyrrolidinone.

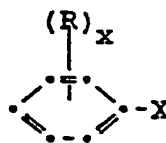
26. The method in accordance with Claim 1 wherein the monohalide has the formula:

15

20

25

30



(I)

wherein one or more of the carbon atoms of the benzene ring in formula (I) is optionally replaced by N;

35

wherein X is a halogen selected from the group consisting of Cl, Br and I;

40

R is a monovalent radical selected from alkyl, aryl, -F, -NR'₂, -CN, -CHO, -OR',

45

-OCO-R', -COO-R', -C(=O)-R', -SO₂-R', -SO₃-R',

or -NR'COR':

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5 wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms, and x is an integer having values of 0 to 4 with the proviso that no more than one R is in a position ortho to the X-containing ring carbon atom.

27. The method according to Claim 26 wherein X is Cl.
28. The method according to Claim 27 wherein said
10 monohalide is selected from the group consisting of:

15 2-chlorotoluene,
2-chloropyridine,
4-fluoro-2-chlorotoluene,
2-chlorobenzyl methyl ether,
2-chlorobenzyl ethyl ether,
4-(N-ethyl-N-acetyl)-2-chlorotoluene,
6-(N-ethyl-N-acetyl)-2-chlorotoluene,
20 4-chlorotoluene,
4-chloroanisole,
2-chlorobenzyl(2-methoxy)ethyl ether,

25 as well as mixtures of any two or more thereof.

29. A method as claimed in Claim 26 wherein R is methyl and x is 1.
30. A method as claimed in Claim 1 wherein the
30 temperature is from about 25°C to about 120°C.
31. The method in accordance with Claim 30 wherein the ratio of gram atoms of nickel to moles of monohalide falls in the range of about 0.01 up to
35 0.2:1; the amount of bidentate

phosphorus-containing ligand falls in the range of about 1 up to 10 moles per gram atom of nickel; and the molar ratio of reducing metal to reactant monohalide falls in the range of about 0.2 up to 10:1.

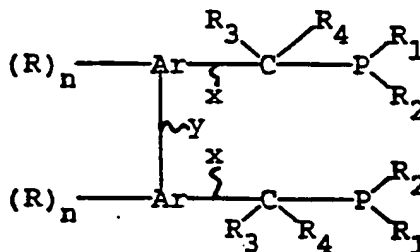
32. The method in accordance with Claim 30 wherein the ratio of gram atoms of nickel to moles of monohalide falls in the range of about 0.03 up to 0.1:1; the amount of bidentate phosphorus-containing ligand falls in the range of about 1 up to 5 moles per gram atom of nickel; and the molar ratio of reducing metal to reactant monohalide falls in the range of about 0.4 up to 5:1.

33. A catalytically active combination comprising:

(I) an anhydrous nickel compound,

(II) at least one bidentate phosphorus-containing ligand selected from the group consisting of

(i)



wherein each Ar is independently selected from aromatic ring compounds having 6 up to 14 carbon atoms;

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the x bonds and the y bonds are attached to adjacent carbon atoms on the ring structures;

5 each R, when present as a substituent, is independently selected from alkyl, aryl, -F, -NR'₂, -CN, -CHO, -OR', -OCO-R',
10 -COO-R', -C(=O)-R', -SO₂-R', -SO₃-R', or -NR'COR':

15 wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms;

20 n is an integer in the range of 0-4 where Ar is phenyl; 0-6 where Ar is naphthyl; and 0-8 where Ar is phenanthryl or anthracenyl;

25 each R₁ and R₂ is independently selected from alkyl, aryl, aralkyl, alkaryl or cycloaliphatic radicals, or substituted derivatives thereof wherein substituted derivatives include ethers, amines, amides, sulfonic acids, esters, hydroxyl groups and alkoxy groups;

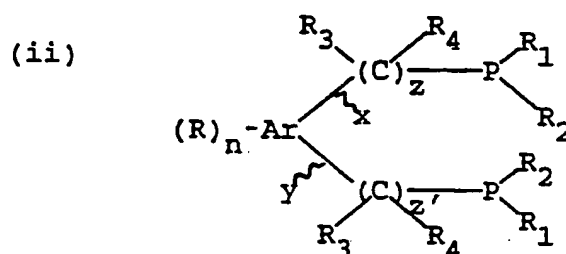
30 each R₃ and R₄ is independently selected from hydrogen and the R₁ substituents;

35 each of the above alkyl groups or moieties is straight or branched chain of 1-20 carbons;

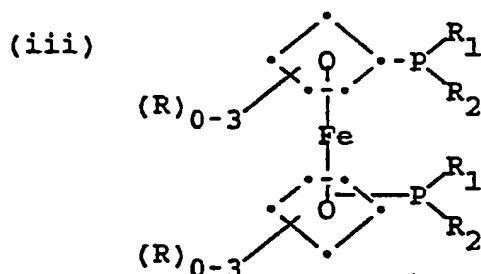
each aryl group contains 4-20 ring carbons; and

- 36 -

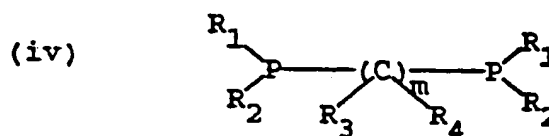
each cycloaliphatic group contains from 4-8 ring carbons;



wherein Ar, x, y, R, n, R₁, R₂, R₃, and R₄ are each as defined above, and each of z and z' can independently vary between 0 and 4, with the proviso that z+z' is at least 2;



wherein R, R₁, and R₂ are as defined above; and



wherein R₁, R₂, R₃ and R₄ are as defined above; and wherein m is a whole number which varies from 5 up to 8;

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as well as mixtures of any two or more of
said type (i), (ii), (iii), or (iv)
organophosphines; and

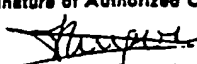
- 5 (III) at least one reducing metal selected from
the group consisting of zinc, magnesium and
manganese;

10 wherein the amount of bidentate
phosphorus-containing ligand falls within the
range of 0.5 up to 20 moles per gram atom of
nickel; and wherein the amount of reducing metal
falls within the range of about 1 up to 1000
moles per mole of nickel.

15

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 89/05218

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁵ : C 07 B 37/04, C 07 C 15/14, 25/18, 43/164, 43/205, IPC ⁵ : C 07 D 213/22, C 07 C 1/26, 17/26, 41/30, C 07 D 213/127		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁵	C 07 B 37/00, C 07 C 1/00, C 07 C 15/00, B 01 J 31/00	
	Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸	
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP, A, 0012201 (UNION CARBIDE)) 25 June 1980, see claims; page 4, lines 17-21 --	1-33
A	The Journal of Organic Chemistry, vol. 51, no. 14, 11 July 1986 American Chemical Society (US) I. Colon et al.: "Coupling of aryl chlorides by nickel and reducing metals" pages 2627-2637 (cited in the application) --	1-33
A	Bulletin of the Chemical Society of Japan, vol. 57, no. 7, July 1984 (JP) K. Takagi et al.: "Ni(0)-trialkyl- phosphine complexes. Efficient homo- coupling catalyst for aryl, alkenyl, and heteroaromatic halides" pages 1887-1890, see the whole article (cited in the application) -----	1-33
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents: 10</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
13th March 1990		12 APR 1990
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		 Mme N. KUIPER

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 89/05218 -2-

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : B 01 J 31/26, //C 07 C 49/784, 69/76, 255/51								
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="height: 40px; vertical-align: top; border-right: 1px solid black;">IPC⁴</td> <td></td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	IPC ⁴			
Classification System	Classification Symbols							
IPC ⁴								
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black;">Category ⁹</th> <th style="width: 60%; border-bottom: 1px solid black;">Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 30%; border-bottom: 1px solid black;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="height: 300px;"></td> <td></td> <td></td> </tr> </table>			Category ⁹	Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³			
Category ⁹	Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³						
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>								
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black;">Date of the Actual Completion of the International Search</td> <td style="width: 50%; border-bottom: 1px solid black;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="border-bottom: 1px solid black; text-align: center;">International Searching Authority EUROPEAN PATENT OFFICE</td> <td style="border-bottom: 1px solid black; text-align: center;">Signature of Authorized Officer</td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report							
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer							

US 8905218
SA 32904

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82